# Synthesis of $C_5$-$C_{18}$ *ansa*-Chain Intermediate Toward the Total Synthesis of Kendomycin

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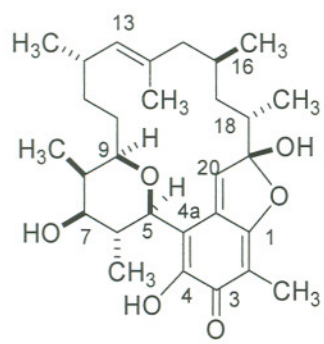
**Introduction**

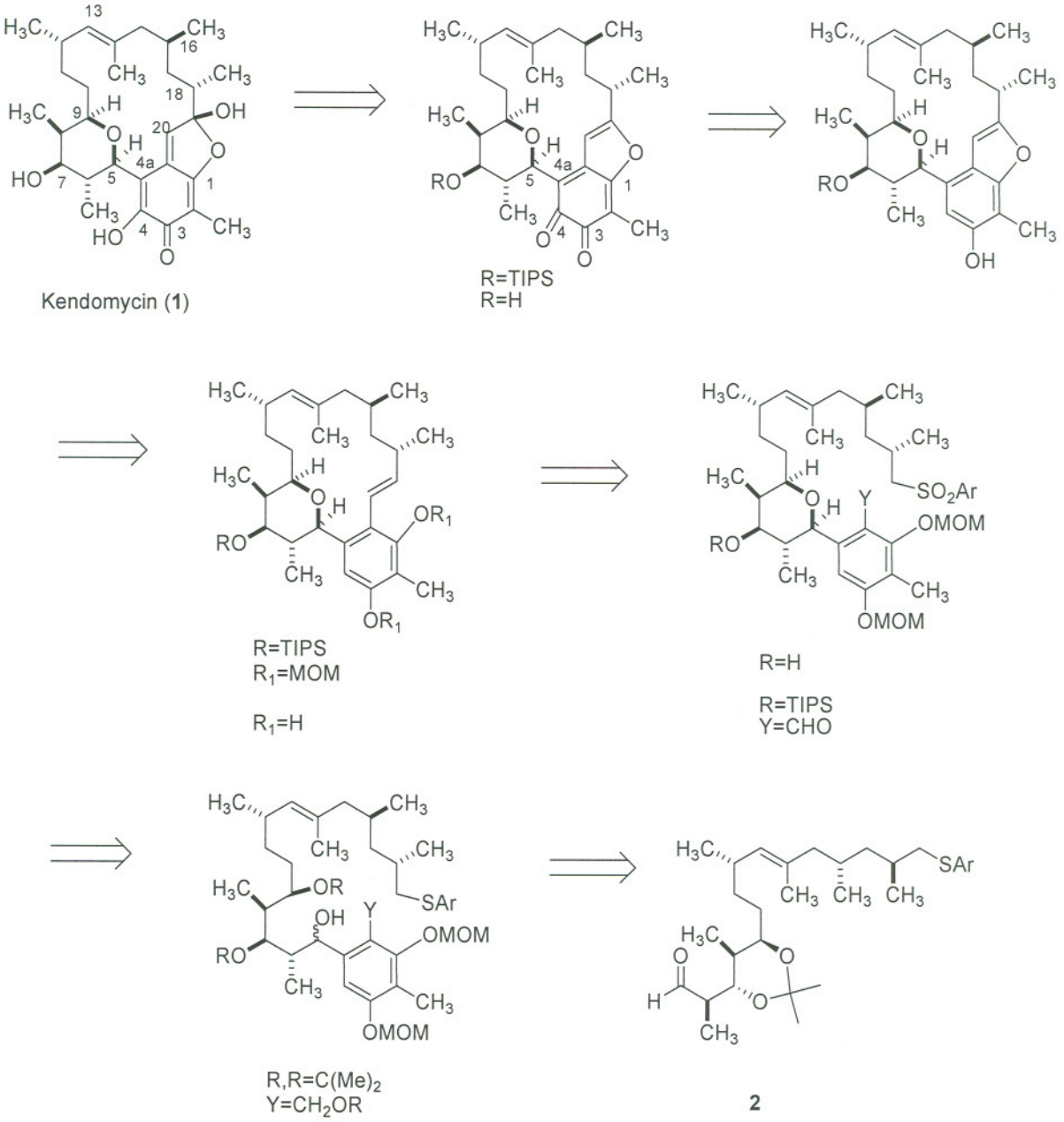
Kendomycin (**1**) is a natural product that has been isolated from the mycelium of *Streptomyces violaceoruber*. It is an antibiotic that has been shown to be a significant anti-tumor agent with activity greater than that of cisplatin and potency similar to doxorubicin when tested against stomach adenocarcinoma (HM02), hepatocelluar carcinoma (HEPG2), and breast adenocarcinoma (MCF7) cell lines[1]. It is also a potent endothelin receptor antagonist[3a] and antiosteoprotic agent[3b]. Kendomycin has shown antibacterial activity against *Staphylococcu aureus* (MRSA) strains and other Gram-positive and Gram-negative organisms. Some of the unique features of the structure include an 18-membered *ansa*-bridged ring and multiple, and in some cases, contiguous stereocenters which pose interesting synthetic challenges. There are currently no reports of proposed synthesis of kendomycin.[1]




Kendomycin (**1**)

## Objective

With the ultimate goal of total synthesis of kendomycin, the following retro-synthetic plan has been proposed (Scheme 1).




Scheme 1. Retro-synthetic plan for kendomycin.

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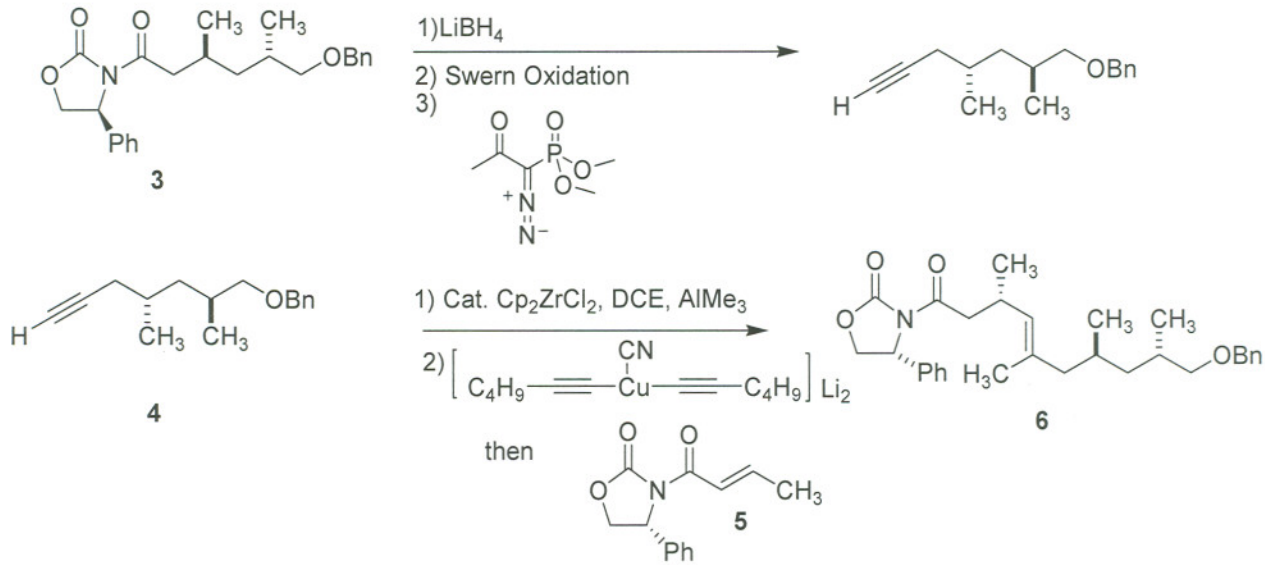
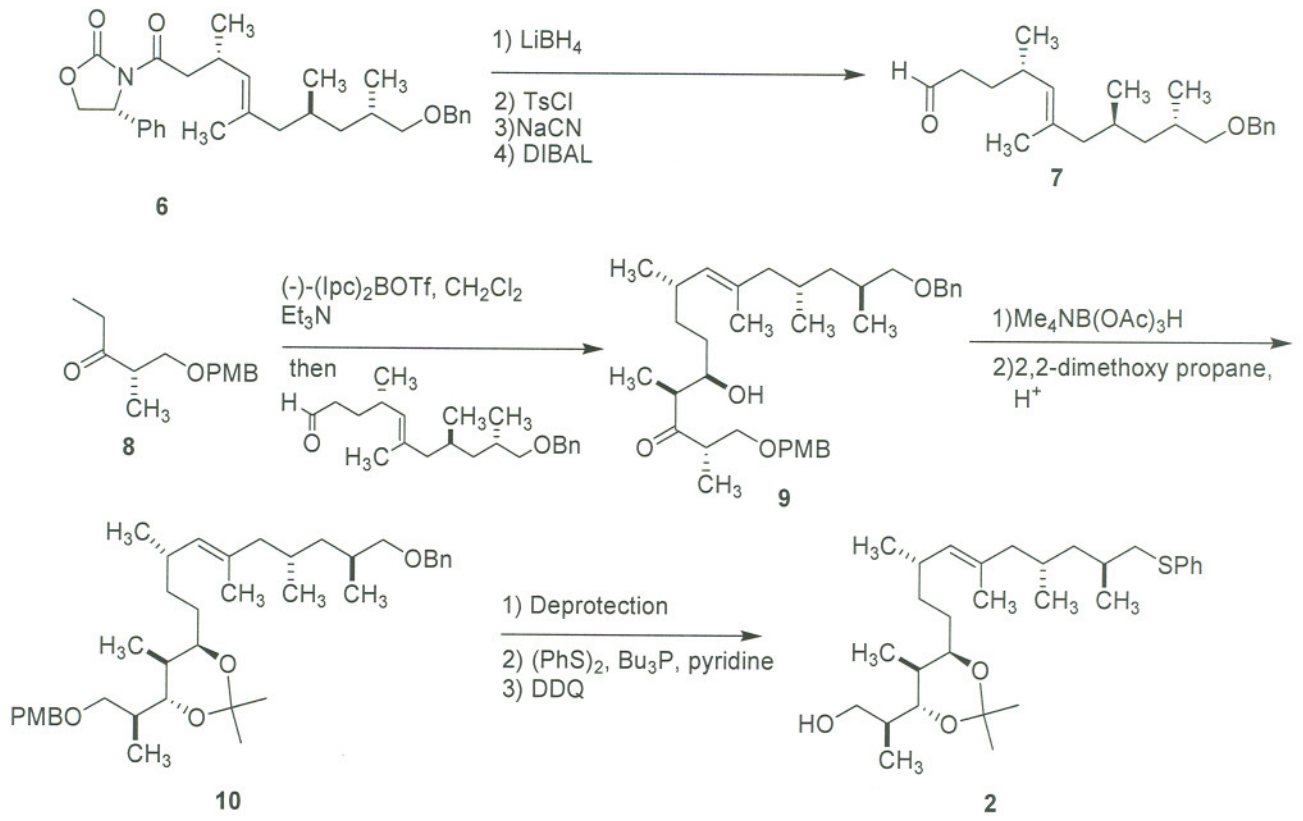
The objective of this project will be to synthesize the important $C_5$-$C_{18}$ *ansa*-chain intermediate **2** to be used in the total synthesis of kendomycin. The following reaction scheme shows the proposed pathway toward producing intermediate **2** (Scheme 2).

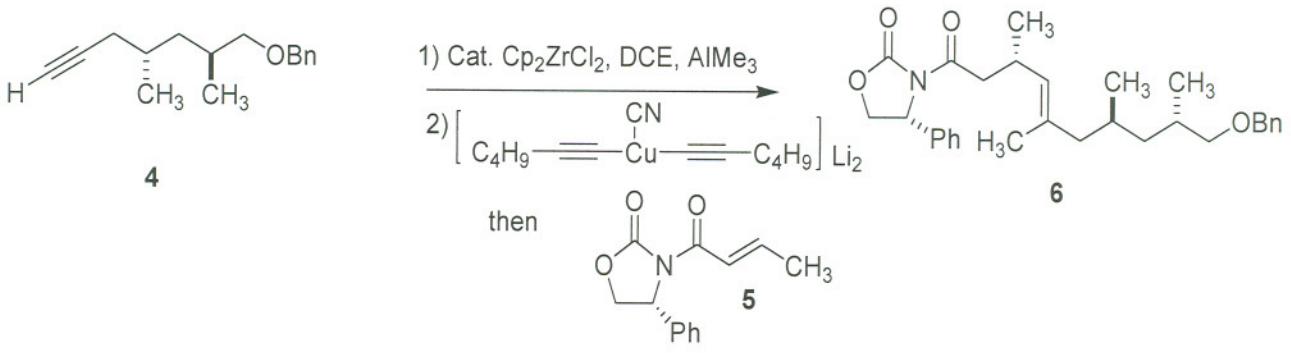
The synthesis of the *ansa*-chain will be based on aspects of William's asymmetric conjugate addition methodology[2]. Swern oxidation of **3**, followed by use of Acyl-DAMP will yield **4**[9]. Transmetallation of **4** following precedents from Lipshutz[5] and Wipf[6] followed by conjugate addition[2] of **5** will lead to product **6**. Aldol reaction[7] with **7** and **8** will produce product **9**. Deprotection of **10**, followed by substitution of phenylthioether for benzyloxy[8] will lead to the desired intermediate **2**.





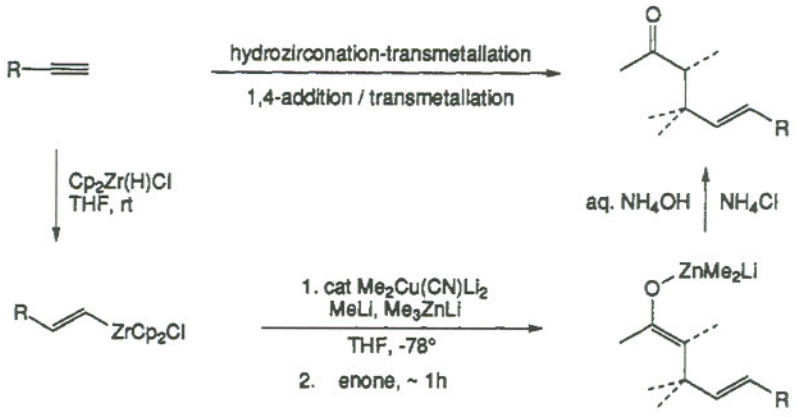

Scheme 2. Synthesis of the $C_5$-$C_{18}$ *ansa*-chain.

In addition to the synthesis of intermediate **2**, the following zirconation reaction will be explored using various alkynyl substrates (Scheme 3).




Scheme 3. Conjugate Addition involving vinylic organometalic and organocopper reagent.

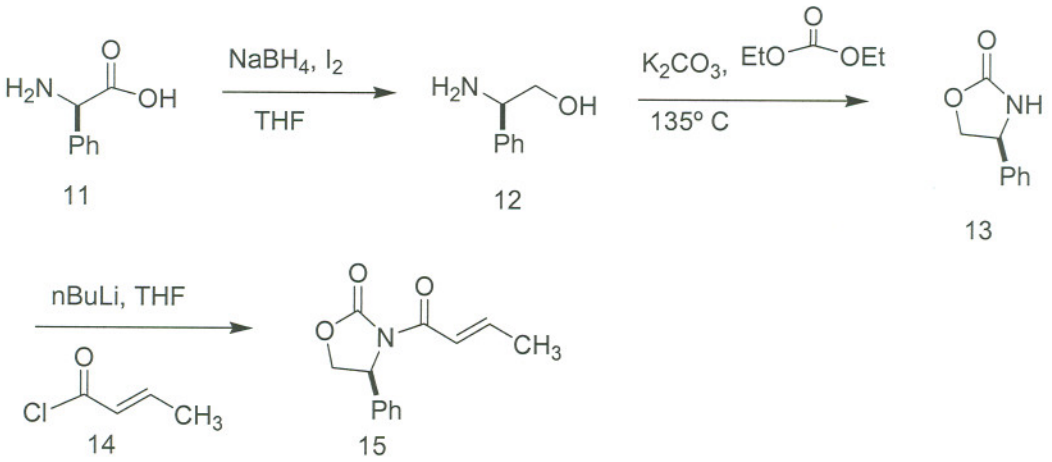
Scheme 3 proceeds throught the following mechanism (Scheme 4).




Scheme 4. Lipshutz, B.H. et al. *J. Am. Chem. Soc.* **1994**, *116*, 11689-11702

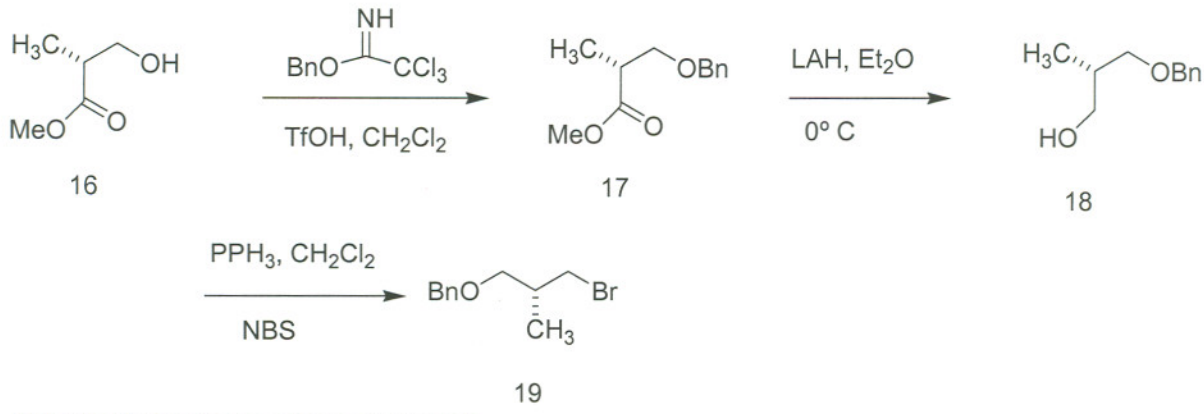
**Completed Work**

The first aspect of research that was completed was to synthesize the oxazolidinone intermediate. The synthesis began with the reduction of phenyl glycine[10] to the corresponding alcohol (**12**, Scheme 5). The alcohol was heated with potassium carbonate and diethyl carbonate at 135°C to distill off ethanol and form the chiral auxiliary **13**[11]. The oxazolidinone intermediate **15** was made by coupling the chiral auxiliary with *trans*-crotonyl chloride[12].




Scheme 5. Synthesis of oxazolidinone.

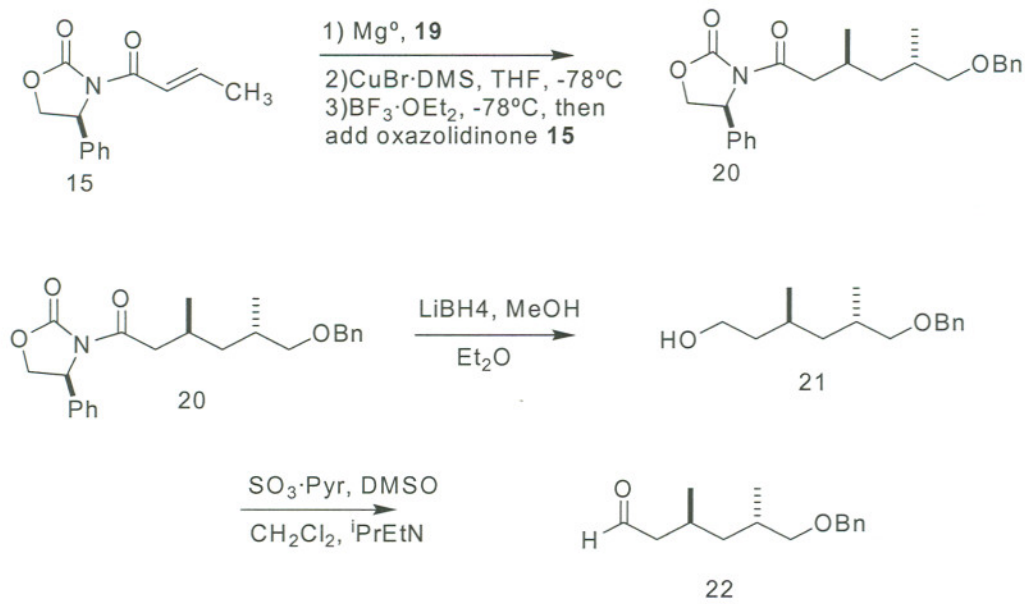
The next phase of the synthesis was to produce a benzyl protected bromide reagent that could later be used to make a Grignard reagent. The synthesis began with a benzyl protection of alcohol **16** (Scheme 6), using benzyl-2,2,2-trichloroacetamidate and triflic acid[13]. The methyl ester **17** was then reduced to alcohol **18**[14] using lithium aluminum hydride. Finally, the bromide **19** was prepared using triphenyl phospine and N-bromosuccinimide[14].




Scheme 6. Synthesis of benzyl bromide.

The bromide was used to form a Grignard Reagent (Scheme 7) using magnesium metal followed by formation of a cuprate using copper bromide·dimethyl sulfide at -78°C[2]. After addition of boron trifloride etherate at -78°C, a conjugate addition of the cuprate and the oxazolidinone **15** was carried out to form intermediate **20**. The chiral auxiliary was removed[15] with lithium borohydride to yield alcohol **21**. Finally, the alcohol was oxidized to the aldehyde **22** using a Parikh-Doering oxidation[16]. The first procedure that was tried was a Swern oxidation; however, the reaction did not go to

completion.




Scheme 7. Conjugate addition and synthesis of aldehyde.

For future work, the synthesis of intermediate **2** will continue as previously described by Scheme 2.

**Experimental Procedures**

**General**

All Nucluear Magnetic Resonance specta were collected on either a Varian GEM-300 or Varian Inova-400 NMR spectrometer. The spectra are described in parts per million (δ) downfield. Deuterated chloroform was used as the solvent for all spectra, and was used as an internal standard (δ 7.26). Thin layer chromatography was done using precoated, glass-backed silica gel plates (0.25 mm thick, EM SCIENCE), and stained with either ethanolic *para*-anisealdehyde or ethanolic potassium permanganate. Kieselgel-60 (230-400 mesh) silica gel (E. Merck) was used for all flash chromatography. Dichloromethane ($CH_2Cl_2$) was distilled from calcium hydride under dry air. Tetrahydrofuran (THF) and diethyl ether ($Et_2O$) were distilled from sodium

benzophenone ketyl under nitrogen. All reactions were carried out in flame dried glassware under argon except where indicated.

11 12

**(R)-2-amino-2-phenylethanol 12**

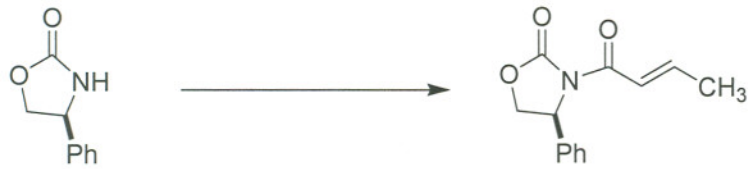
To a mixture of phynyl glycine (50 g, 331 mmol) in THF (450 mL) was added $NaBH_4$ (30 g, 794 mmol). The mixture was cooled to 0°C and a solution of $I_2$ (84 g, 331 mmol) in THF (210 mL) was added dropwise over 1.5 h. The ice bath was removed and mixture was heated to 42°C until evolution of gas was complete. The mixture was heated to reflux for 18 h. The reaction was cooled to rt and quenched with MeOH (250 mL). After evolution of gas, mixture was concentrated to a white paste. KOH (20% by mass) was added to mixture and stirred overnight. Mixture was extracted with $CH_2Cl_2$ (4 x 500 mL), dried over $Na_2SO_4$, filtered, and concentrated. The solid was recrystallized from hot toluene to form white crystals: yield:16.69 g (36.8%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 5H), 3.97 (dd, J=4.3 Hz, 1 H), 3.67 (dd, A of ABX, $J_{AB}$=10.7 Hz, $J_{AX}$=4.39 Hz), 3.47 (B of ABX, $J_{AB}$=10.7 Hz, $J_{BX}$=8.51 Hz, 1H), 1.66 (br s, 2H)

**12** **13**

**(S)-4-phynyloxazolidin-2-one 13**

To a dry 250 mL round bottom w/ stirbar, alcohol **12** (7.76 g, 56.6 mmol) was added. The $K_2CO_3$ (0.78 g, 5.66 mmol) was added in one portion. The diethyl carbonate (14.12

mL, 116.59 mmol) was poured from a dry graduated cylinder. A six inch Vigreaux column was attached. A condenser with 100 mL rb collection flask was attached in a 0°C ice bath. The reaction mixture was taken to 135°C via oil bath. After cessation of ethanol distillation, the mixture was cooled to rt, diluted with $CH_2Cl_2$, and washed with $H_2O$. The aqueous layer was back-extracted with $CH_2Cl_2$ (2 x 200 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated to an off-white solid. The flask was placed under vacuum overnight. The solid was transferred to 500 mL Erlenmeyer flask and recrystallized from hot 2:1 EtOAc: Hexanes: yield 6.04 g (65.4%); 1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.26 (m, 5H), 5.34 (2, 1H), 4.96 (dd, A of ABX, $J_{AB}$=7.7, $J_{AX}$=7.8 Hz, 1H), 4.75 (t, J=8.6, 1H), 4.20 (dd, B of ABX, $J_{AB}$=8.1, $J_{BX}$=7.1, 1H)




**13** **15**

**(*S*,*E*)-3-but-2-enoyl-4-phenyloxazolidin-2-one 15**

Oxazolidinone **13** (1.00 g, 6.13 mmol) was taken in THF and cooled to -78°C. $^{n}$BuLi (2.5 M in hexanes, 2.94 mL, 7.35 mmol) was added dropwise over 10 min. The reaction mixture turned yellow and was stirred for 30 min. Crotonyl chloride was added dropwise over 15 min. Reaction mixture stirred for 1 h at -78°C and warmed gradually to rt. After 5 h, reaction was quenched with sat. aq. $NH_4Cl$ and diluted with $Et_2O$. Water was added and layers were separated. Aqueous layers were extracted with $Et_2O$. Organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography yielded **15**: yield 1.01 g (71%); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.62-7.46 (m, 6H), 7.36-7.24 (m, 1H), 5.69 (dd, A of ABX, $J_{AB}$=8.7, $J_{AX}$=3.85 Hz, 1H), 4.91 (t,

J=8.79 Hz, 1H), 4.48 (dd, B of ABX, $J_{AB}$=8.7, $J_{BX}$=3.92 Hz, 1 H), 2.14 (dd, J=6.9, 1.5 Hz, 3H)


**16** **17**

**(*R*)-methyl 3-(benzyloxy)-2-methylpropanoate 17**

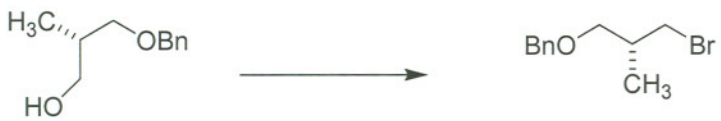
To a rt solution of alcohol **16** (5.00g, 42.3 mmol) in $CH_2Cl_2$ (90 mL) was added benzyl-2,2,2-trichloroacetamidate (28.3 mL, 63.5 mmol) and triflic acid (224.1 μL, 1.27 mmol). The reaction mixture was stirred for 15 min at rt. The mixture was quenched with 200 mL $NaHCO_3$, and stirred for 30 min. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 150 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel column. Elution with 5% EtOAc in Hexanes yielded **17**: yield 7.63 g (86.6%); silica gel TLC (33% EtOAc in Hex); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.28-7.20 (m, 5H), 5.24, (s, 2H), 3.63 (s, 3H), 3.61 (dd, A of ABX, $J_{AB}$=13.2, $J_{AX}$=8.4, 1H), 3.44 (dd, B of ABX, $J_{AB}$=13.7, $J_{BX}$=5.8, 1H), 2.79-2.62 (m, 2H), 1.12 (d, J=7.1 Hz, 3H)


**17** **18**

**(*S*)-3-(benzyloxy)-2-methylpropan-1-ol 18**

To $Et_2O$ (60 mL) at 0°C was added LAH (1.67 g, 43.97 mmol). A solution of propionate **17** (7.63 g, 36.64 mmol) in $Et_2O$ (60 mL) was then added dropwise to the 0°C LAH

suspension. After stirring for 30 min at 0°C, TLC indicated no starting material remaining. Reaction was quenched at 0°C with $H_2O$ (5 mL) and stirred for 5 min. Reaction mixture was warmed to rt and stirred with $Na_2SO_4$ for 1 hr. Solids were filtered via sintered glass funnel, and filtrate was concentrated. The crude product was purified via flash chromatography on silica gel column. Elution with 20% EtOAc in hexanes gave **18**: yield 5.21 g (78.9%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.27-7.18 (m, 5H), 4.45 (s, 2H), 3.59-3.46 (m, 3H), 3.36 (t, J=8.3 Hz, 1H), 1.51 (d, J=13.7 Hz, 1H), 1.19 (t, J=7.1 Hz, 1H), 0.79 (d, J=7.0 Hz, 3H)

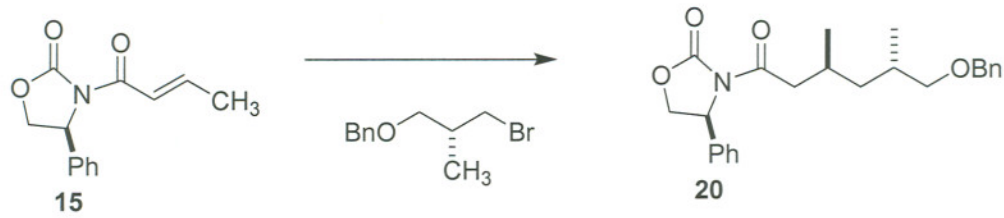



**18** **19**

**(*R*)-((3-bromo-2-methylpropoxy)methyl)benzene 19**

To a solution of alcohol **18** (4.62 g, 25.63 mmol) in $CH_2Cl_2$ (51.26 mL) was added $PPh_3$ (7.06 g, 26.91 mmol). The solution was cooled to 0°C and NBS (4.79 g, 26.91 mmol) was added in four portions over 10 min. The clear yellow solution was warmed to rt, covered with foil, and stirred overnight. Solution was washed with 5% aq. $NaHCO_3$ (100 mL) and concentrated to a blue solid. The solid was treated with hexanes (250 mL) and $H_2O$ (250 mL) and stirred at rt for 20 min. The solid was filtered and washed with hexanes. The organic layer was separated from the aqueous later, dried with $MgSO_4$, filtered, and concentrated. The crude product was purified via flash chromatography on silica gel column. Elution with 1% $Et_2O$ in hexanes gave **19**: yield 5.56 g (89.2%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.28-7.20 (m, 5H), 4.50 (s, 2H), 3.43 (dd, A of ABX,

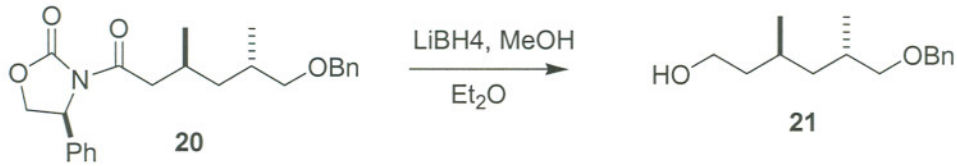
$J_{AB}$=23.6, $J_{AB}$=5.5 Hz, 1H), 3.43 (dd, A of ABX, $J_{AB}$=5.5, $J_{AX}$=3.88 Hz, 1H), 3.34 (dd, B of ABX, $J_{AB}$=23.3, $J_{BX}$=6.0 Hz, 1H), 3.34 (B of ABX, $J_{AB}$=4.88, $J_{BX}$=3.9 Hz, 1H), 2.10-2.01 (m, 1H), 1.02 (d, J=6.8 Hz, 3H)




**(*S*)-3-((3*S*,5*S*)-6-(benzyloxy)-3,5-dimethylhexanoyl)-4-phenyloxazolidin-2-one 20**

The bromide **19** (1.00 g, 4.11 mmol) was azeotroped, via rotary evaporator, with toluene (2 x 1.5 mL). To Mg turnings (0.999 g, 41.12 mmol, crushed and flame dried) was added THF (1.06 mL) and 1 drop of dibromoethane followed by the bromide in THF (6 mL) slowly enough to maintain a gentle reflux. Mixture was stirred at reflux for 30 min and then cooled to rt. Grignard solution was added via canula to a solution of CuBr·DMS (0.8453 g, 4.11 mmol) in THF (4.5 mL) at -78°C. DMS (1 mL) was added to reaction mixture at -78°C. The mixture was warmed to -30°C, stirred for 30 min, then cooled to -78°C (solution turned yellowish brown). $BF_3{\cdot}OEt_2$ (0.521 mL, 4.11 mmol) was added, solution was stirred for 5 min, then oxazolidinone (0.475 g, 2.06 mmol) in THF (4.5 mL) was added. The mixture was stirred for 3 h at -78°C, and placed in -20°C freezer overnight. The reaction was quenched with sat. $NH_4Cl$ (25 mL) and diluted with $Et_2O$. The aqueous layer was extracted with $Et_2O$ (3 x 25 mL). The combined organic layers were washed with $H_2O$ (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. The crude compound was purified using flash chromatography on silica gel column. Elution with 20% EtOAc in hexanes gave compound **20**: yield 0.397 g

(48.8%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (m, 10H), 5.43 (dd, A of ABX, $J_{AB}$=8.6, $J_{AX}$=3.6 Hz, 1H), 4.68 (t, J=9.3 Hz, 1H), 4.47 (s, 2H), 4.27 (dd, B of ABX, $J_{AB}$=8.8, $J_{BX}$=3.39 Hz, 1H), 3.27-3.18 (m, 2H), 2.95 (dd, A of ABX, $J_{AB}$=16.1, $J_{AX}$=5.18 Hz, 1H), 2.73 (dd, B of ABX, $J_{AB}$=16..4, $J_{BX}$=8.5 Hz, 1H), 2.09 (m, 1H), 1.85-1.80 (m, 1H), 0.853 (dd, J=6.8, 2.9 Hz, 6H)




20 21

**(3*S*,5*S*)-6-(benzyloxy)-3,5-dimethylhexan-1-ol 21**

To a solution 0°C solution of oxazolidinone **20** (0.846 g, 2.18 mmol) in $Et_2O$ (10.9 mL) was added MeOH (0.177 mL, 4.37 mmol) and $LiBH_4$ (0.0952 g, 4.37 mmol). The reaction mixture was stirred at 0°C for 10 min. Reaction was quenched with $NaHCO_3$ and warmed to rt. The mixture was diluted with $Et_2O$ and washed with $NaHCO_3$. Organic layer was dried over anhyd. $Na_2SO_4$, filtered, and concentrated. The crude product was purified using flash chromatography on a silica gel column. Elution in 25% EtOAc in hexanes gave product **21**: yield 0.225 g (44%)


21 22

**(3*S*,5*S*)-6-(benzyloxy)-3,5-dimethylhexanal 22**

Alcohol **21** (0.0272 g, 1.15 mmol) was dissolved in $CH_2Cl_2$ (0.408 mL) in a flame dried flask. In separate flask, $SO_3$·Pyr (0.0549 g, 3.45 mmol) was dissolved in DMSO (0.108 mL). The alcohol was cooled to 0°C and Hunig's base (0.0583 mL, 3.45 mmol) was added. The solution of $SO_3$·Pyr was then added slowly. The reaction mixture was stirred

for 15 min at 0°C. The solution was diluted with $CH_2Cl_2$ and washed with brine, $NaHCO_3$, $H_2O$, and sat. $CuSO_4$. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a pale yellow liquid. The crude compound was purified by flash chromatography using silica gel column. Elution with 20% EtOAc in hexanes gave compound **22**.

**References**

(1) Bode, H.B.; Zeeck, A. Structure and Biosynthesis of Kendomycin, a Carbocyclic *ansa*-Compound from *Strptomyces*, *J.Chem Soc., Perkin Trans. 1*, **2000**, 323-328.
(2) a) Williams, D. R.; Kissel, W. S.; Li, J.J.; Mullins, R.J. Stereoselective Synthesis of *syn*- and *anti*-1,3-and 1,2-Dimethyl Arrays via Asymmetric Conjugate Additions, *Tetraheron Lett.* **2002**, *43*, 3723-3727.
b) Williams, D.R.; Kissel, W.S.; Li, J.J. Diastereoselection in the Conjugate Additions of Organocopper Reagents to N-Enoyloxazolidinones, *Tetrahedron Lett.* **1998**, *39*, 8593-8596. c) Han, Y.; Hruby, V.J. Lewis Acid Promoted Conjugate Addition of Vinylmagnesium Bromide to Chiral α,β-Unsaturated N-Acyl Oxazolidinones, *Tetrahedron Lett.* **1997,** *38*, 7317-7320.
(3) a) Funahashi, Y.; Kawamura, N.; Ishimaru, T. *Jap. Pat.* 08 231 551 [A2 960 910], 1996 (*Chem. Abstr.* **1997**, *126*, 6553). Funahashi, Y.; Ishimaru, T.; Kawamura, N. *Jap. Pat.* 08 231 552 [A2 960910], 1996 (*Chem. Abstr.* **1996**, *125* 326518).
b)Su, M.H.; Hosken, M.I.; Hotovec, B.J.; Johnston, T.L. *U.S. Pat.* 5 728 727 [A 9803 17] 1998 (*Chem. Abstr.* **1998**, *128*, 239489).
(4)
(5) Lipshutz, B.H.; Wood, M.R. *J. Am. Chem. Soc.***1994**, *116*, 11689-11702.
(6) Wipf, P.; Takahashi, H. *Chem. Commun.* **1996**, 2675-2676.
(7) a) Cowden, C.J.; Patterson, I. *Org. React.* **1997**, *51*, 1. b) Franklin, A.S.; Patterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317. c) Patterson, I; Goodman, J.M.; Lister, M.A.; Schumann, R.C.; McClure, C.K.; Norcross, R.D. *Tetrahedron*, **1990**, *46*, 4663-4684.
(8) Keyserlingk, N.G.; Martens, J. *Tetrahedron: Asymmetry*. **2001**, *12*, 2213-2222.
(9) a) Muller, S.; Liepold, B.; Roth, G.J.; Bestmann, H.J. *Sylett.* **1996**, 521-522.
b) Ohira, S. *Synth. Commun.* **1989**, *19*, 561
(10) McKennon, M. J. et al. *J. Org. Chem*. **1993**, *58*, 3568-3571.
(11) Janey, J. M. et al. *J. Org. Chem.* **2000**, *65*, 9050-9068.
(12) Dambacher, J. et al. *Tetrahedron*, **2004**, *60*, 2097-2110.
(13) Keck, G. E. et al. *J. Org. Chem.* **1994**, *59*, 3113-3122.
(14) White, J. D. et al. *J. Org. Chem.* **1994**, *59*, 3347-3358.
(15) Williams, D. R. et al. *Tetrahedron Lett.* **2000**, *41*, 9397-9402.
(16) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507